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ORIGINAL RESEARCH

Thermochemistry of drugs: experimental and theoretical study of analgesics

Ruslan N. Nagrimanov[1] · Marat A. Ziganshin[1] · Boris N. Solomonov[1] · Sergey P. Verevkin[2,3]

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Abstract

Acetanilides are broadly used in the pharmaceutical industry. Thermochemical data on vapor pressures, solid-gas, liquid-gas, and solid-liquid phase transitions, as well as on enthalpies of formation of substituted acetanilides have been collected and evaluated with help of additional experimental measurements. Absolute vapor pressures of *meta*- and *para*-substituted acetanilides were studied by using transpiration method. Significant disagreement of available literature data on isomeric hydroxyacetanilides was detected and resolved. A quick estimation scheme of vaporization enthalpies of substituted acetanilides at 298.15 K was developed based on "structure-property" relationships. Quantum-chemical methods were applied for calculation of theoretical gas-phase enthalpies of formation of substituted acetanilides. Theoretical values together with results from "structure-property" analysis allowed for validation of the experimental crystalline state enthalpies of formation and prediction of these values based on quantum-chemical calculations.

Keywords Acetanilide derivatives · Vapor pressures, enthalpy of sublimation · Enthalpy of vaporization, enthalpy of fusion

Introduction

Substituted acetanilides are known for their biological activity [1, 2]. Some of them are effective analgesics [3, 4]. These properties are a consequence of the structural peculiarities specific for this class of compounds. In this context, a study of "structure-property" relationships is an important tool for understanding and predicting properties of chemical compounds and drugs.

Synthesis and practical application of drugs require knowledge of thermochemical properties of pure acetanilides. However, due to low volatility and restricted thermal stability the determination of phase transitions enthalpies are thwarted by different complications [5], even for well-established methods like the Knudsen effusion method [6–9], the transpiration method [10–13], drop-calorimetry [7], solution calorimetry [14], thermogravimetry, and DSC [15, 16]. Moreover, the spread of available values is large and it makes setting of preferences difficult. For example, for the series of hydroxyacetanilides, we found a significant disagreement as follows: for 2′-hydroxyacetanilide (from 122.5 kJ mol^{-1} [10] to 137.4 kJ mol^{-1} [15]), 3′-hydroxyacetanilide (from 111.8 kJ mol^{-1} [10] to 127.9 kJ mol^{-1} [14]), and 4′-hydroxyacetanilide (from 118.8 kJ mol^{-1} [11] to 129.0 kJ mol^{-1} [7]). Also, absolute vapor pressures of 4′-hydroxyacetanilide, reported by the transpiration method [11] and from the Knudsen effusion method [7] are in total disagreement and additional experimental studies are required. In recent works, we used "structure-property" relationship, in order to establish consistency of experimental thermochemical values (enthalpies of vaporization and formation) for substituted benzenes [17, 18]. This experience is utilized in similar fashion with regard to the thermochemistry of substituted acetanilides. Available experimental values on

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✉ Ruslan N. Nagrimanov
rnagrimanov@gmail.com

✉ Sergey P. Verevkin
sergey.verevkin@uni-rostock.de

[1] Department of Physical Chemistry, Kazan Federal University, Kremlevskaya str. 18, 420008 Kazan, Russia

[2] Chemical Department, Samara State Technical University, 443100 Samara, Russia

[3] Department of Physical Chemistry, University of Rostock, 18059 Rostock, Germany